REMARKS

Unity of Invention

On page 2 of the Office Action, in paragraph 2, the Examiner indicates that newly submitted claims 11-19 are directed to an invention that lacks unity with the invention originally claimed, because the technical feature of a thiazole derivative of formula I and an additive is not a special technical feature as it does not make a contribution over the prior art in view of the prior art rejection presented below under 35 USC 103. Since Applicant has received an action on the merits for the originally presented invention, the Examiner indicates that this invention has been constructively elected by original presentation for prosecution on the merits, and thus claims 11-19 are withdrawn from consideration as being directed to a nonelected invention.

In response, Applicants respectfully request rejoinder of claims 11-19 upon a finding of allowable subject matter in claim 1 pursuant to MPEP 821.04(b), since claim 11 includes all the requirements of claim 1.

Obviousness Rejection

On page 3 of the Office Action, claims 1-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Inoue, et al. (WO 2004/067521 Al; priority date 2003 Jan 27; IDS March 30, 2007, reference) and Ogata et al. (US 4,780,465; 1988); in view of Niebergall (Ionic Solutions and Electrolytic Equilibria; 2000; "Remington: The Science and Practice of Pharmacy"; 20th Ed.; Gennaro, Ed.; Lippincott Williams & Wilkins; Chapter 17, pp. 227-245).

In response, Applicants submit initially that the newly cited reference Niebergall teaches that "[t]he aqueous solubility of a slightly soluble organic substance generally is affected

markedly by the addition of an electrolyte." However, this is not applicable to the compound of the instant application.

According to Niebergall, the salting out effect is particularly noticeable when the electrolyte concentration reaches 0.5M or higher" (see page 231, left column, just below "SALTING-OUT EFFECT"), and as examples of "slightly soluble organic substance", barbiturates are disclosed in Table 17-3. According to Table 17-3, all barbiturates have salting out constants that fall within a very small range.

In the meantime, the term "slightly soluble" is defined in the attached General Notices part of the US Pharmacopeia and is determined based on to parts of solvent required for 1 part of solute. According to the General Notices, "slightly soluble" means "from 100 to 1000 parts of solvent per 1 part of solute" and that corresponds to the concentration range of the solute in the solvent dose of 1 mg/m1-10mg/ml.

In terms of the compound of the instant invention, please see Table 1 on page 37 of the specification. According to this table, Compounds A, B and C are "slightly soluble" materials since the solubility in water (i.e., concentration when NaC1=0) of those compounds were Compound A=3.55mg/ml, B=1.12mg/ml and C=10.73mg/ml. Compounds A and C were precipitated (salted out) at the NaC1 concentrations of 0.4% and 0.85%, while Compound B was not. The concentrations of NaC1 at which Compounds A and C were precipitated (0.4% and 0.85%) correspond to 0.068M and 0.14M respectively. That is, Compounds A and C were precipitated by a concentration of NaCl significantly lower than 0.5M. This fact explains that Niebergall is not applicable to the compound of the instant claims.

As the Examiner indicated, Compound A, B and C are disclosed in Inoue. As discussed above, all of those compounds are "slightly soluble" compounds, but the effect of NaC1 on the

solubility of those compounds is different. Inoue does not even suggest this fact. Accordingly, Applicants submit that one of ordinary skill in the art would not have come up with the idea of the instant claims based on combination of Inoue and Niebergall.

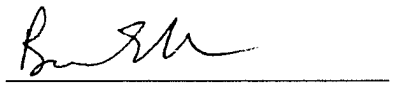
Thus, Applicants submit that the present invention is not obvious over the cited art, and withdrawal of this rejection is respectfully requested.

Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



Bruce E. Kramer
Registration No. 33,725

SUGHRUE MION, PLLC
Telephone: (202) 293-7060
Facsimile: (202) 293-7860

WASHINGTON OFFICE
23373
CUSTOMER NUMBER

Date: October 8, 2009

General Notices and Requirements

Applying to Standards, Tests, Assays, and Other Specifications of the United States Pharmacopeia

The air in a container of an official article may, where appropriate, be evacuated or be replaced by carbon dioxide, helium, argon, or nitrogen, or by a mixture of these gases. The use of such gas need not be declared in the labeling.

5.20.10. Added Substances, Excipients, and Ingredients in Official Substances

Official substances may contain only the specific added substances that are permitted by the individual monograph. Where such addition is permitted, the label shall indicate the name(s) and amount(s) of any added substance(s).

5.20.20. Added Substances, Excipients, and Ingredients in Official Products

Suitable substances and excipients such as antimicrobial agents, pharmaceutical bases, carriers, coatings, flavors, preservatives, stabilizers, and vehicles may be added to an official product to enhance its stability, usefulness, or elegance, or to facilitate its preparation, unless otherwise specified in the individual monograph.

Added substances and excipients employed solely to impart color may be incorporated into official products other than those intended for parenteral or ophthalmic use, in accordance with the regulations pertaining to the use of colors issued by the U.S. Food and Drug Administration (FDA), provided such added substances or excipients are otherwise appropriate in all respects. (See also *Added Substances* under *Injections* ⟨1⟩.)

The proportions of the substances constituting the base in ointment and suppository products and preparations may be varied to maintain a suitable consistency under different climatic conditions, provided that the concentrations of active ingredients are not varied and provided that the bioavailability, therapeutic efficacy, and safety of the preparation are not impaired.

5.20.20.1. In Compounded Preparations

Compounded preparations for which a complete composition is given shall contain only the ingredients named in the formulas unless specifically exempted herein or in the individual monograph. Deviation from the specified processes or methods of compounding, although not from the ingredients or proportions thereof, may occur provided that the finished preparation conforms to the relevant standards and to preparations produced by following the specified process.

Where a monograph for a compounded preparation calls for an ingredient in an amount expressed on the dried basis, the ingredient need not be dried before use if due allowance is made for the water or other volatile substances present in the quantity taken.

Specially denatured alcohol formulas are available for use in accordance with federal statutes and regulations of the Internal Revenue Service. A suitable formula of specially denatured alcohol may be substituted for Alcohol in the manufacture of official preparations intended for internal or topical use, provided that the denaturant is volatile and does not remain in the finished product. A preparation that is intended for topical application to the skin may contain specially denatured alcohol, provided that the denaturant is either a usual ingredient in the preparation or a permissible added substance; in either case the denaturant shall be identified on the label of the topical preparation. Where a process is given in the individual monograph, any preparation compounded using denatured alcohol shall be identical to that prepared by the monograph process.

5.20.20.2. In Dietary Supplements

Additional ingredients may be added to dietary supplement products provided that the additional ingredients: (1) comply with applicable regulatory requirements; and (2) do not interfere with the assays and tests prescribed for determining compliance with compendial standards.

5.30. Description and Solubility

Only where a quantitative solubility test is given in a monograph and is designated as such is it a test for purity.

A monograph may include information regarding the article's description. Information about an article's "description and solubility" also is provided in the reference table *Description and Relative Solubility of USP and NF Articles*. The reference table merely denotes the properties of articles that comply with monograph standards. The reference table is intended primarily for those who use, prepare, and dispense drugs and/or related articles. Although the information provided in monographs and the information in the reference table may indirectly assist in the preliminary evaluation of an article, it is not intended to serve as a standard or test for purity.

The approximate solubility of a compendial substance is indicated by one of the following descriptive terms:

Descriptive Term	Parts of Solvent Required for 1 Part of Solute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1,000
Very slightly soluble	From 1,000 to 10,000
Practically insoluble, or Insoluble	Greater than or equal to 10,000

5.40. Identification Test

The compendial test titled *Identification* is provided as an aid in verifying the identity of articles as they are purported to be, e.g., those taken from labeled containers. Tests presented in the *Identification* section shall be used to assist in establishing the identity of the substance but are not necessarily sufficient to establish proof of identity. Other tests and specifications in the monograph often are necessary to establish or confirm the identity of an article. Failure of an article to meet the requirements of a prescribed *Identification* test may indicate that the article is mislabeled.

5.50. Assay

Assay tests for compounded preparations are not intended for evaluating a compounded preparation before dispensing, but instead are intended to serve as the official test in the event of a question or dispute regarding the preparation's conformance to official standards.

5.50.10. Units of Potency (Biological)

For substances that cannot be completely characterized by chemical and physical means, it may be necessary to express quantities of activity in biological units of potency, each defined by an authoritative, designated reference standard.

Units of biological potency defined by the World Health Organization (WHO) for International Biological Standards and International Biological Reference Preparations are termed International Units (IU). Monographs refer to the units defined by USP Reference Standards as "USP Units." For biological products, units of potency are defined by the corresponding U.S. Standard established by FDA, whether or not International Units or USP Units have been defined (see *Biologics* ⟨1041⟩).

5.60. Impurities and Foreign Substances

Tests for the presence of impurities and foreign substances are provided to limit such substances to amounts that are unobjectionable under conditions in which the article is customarily employed (see also *Impurities in Official Articles* ⟨1086⟩).

Nonmonograph tests and acceptance criteria suitable for detecting and controlling impurities that may result from a change in the processing methods or that may be introduced from external sources should be employed in addition to the tests provided in the individual monograph, where the presence of the impurity is inconsistent with applicable good manufacturing practices or good pharmaceutical practice.

5.60.10. Other Impurities in *USP* and *NF* Articles

If a *USP* or *NF* monograph includes an assay or organic impurity test based on chromatography, other than a test for residual solvents, and that monograph procedure does not detect an impurity present in the substance, the amount and identity of the impurity, where both are known, shall be stated in the labeling (certificate of analysis) of the official substance, under the heading *Other Impurity(ies)*.

The presence of any unlabeled other impurity in an official substance is a variance from the standard if the content is 0.1% or greater. The sum of all *Other Impurities* combined with the monograph-detected impurities may not exceed 2.0% (see *Ordinary Impurities* ⟨466⟩), unless otherwise stated in the monograph.

The following categories of drug substances are excluded from *Other Impurities* requirements: